OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 59-65, 71, 86, and 93 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 of U.S. Patent No. 5,980,896 (Hellström et al.). The Action asserts that the pending claims are not patentably distinct from the issued claims because the issued claims are directed to a species of antibody that may be used for making an immunoconjugate according to the instant claims as drawn to an immunoconjugate genus, in a manner that renders the genus obvious.

Applicants respectfully traverse this ground for rejection and submit that the present claims satisfy all requirements for patentability. Nevertheless, without acquiescing in the double patenting rejection, at such time as the claims in the present application are acknowledged by the Examiner to be otherwise allowable, applicants will timely file a terminal disclaimer in compliance with 37 C.F.R. §1.32(c), thereby obviating the double patenting rejection.

REJECTION UNDER 35 U.S.C. § 103

Claims 59-65, 71, 86, and 93 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Abe et al. (1986 *Cancer Res.* 46:2639), Kim et al. (1986 *Cancer Res.* 46:5985 ), and Hellström et al. (1986 *Cancer Res.* 46:3917). More specifically, the Action asserts that Abe et al. and Kim et al. teach a monoclonal antibody that reacts with a fucosylated Lewis Y antigen marker of colorectal cancer, and that Hellstrom et al. teach screening monoclonal antibodies for tumor selectivity. The Action concedes that these references do not teach immunoconjugates, but asserts that Oldham et al. (a reference not fully cited in the Action, nor in the accompanying Information Disclosure Statement, but presumed to be 1983 *J. Biol. Resp. Modif.* 2:1-37 based on reference in the Action to "pgs 13-14") teach monoclonal antibody-derived immunoconjugates for use in diagnosis and treatment of cancer, and further that Schlom (also not fully cited in the Action, but assumed to be entry "KF" on Sheet 11 of the IDS, based on the reference to "page 115") teaches the use of immunoconjugates for specific delivery of therapeutic agents. The Action then alleges that a person having ordinary skill in the art would have found it obvious to combine (i) Lewis Y antigen-specific antibodies of

Abe et al., Kim et al. and Hellstrom et al. with (ii) immunoconjugate methodologies taught by Oldham et al. and Schlom, to arrive at the claimed invention.

Applicants respectfully traverse these grounds for rejection and submit that the references cited by the Action, alone or in combination, fail to teach or suggest the subject matter of the instant claims. The present invention is directed, in pertinent part, to an immunoconjugate that comprises an antibody joined to a therapeutic agent, wherein the antibody comprises an immunogloblulin or antigen-binding fragment thereof that specifically binds to a Lewis Y cell membrane antigen of a carcinoma cell, wherein upon binding of the antibody to the carcinoma cell, the antibody is capable of being internalized within the cell. Applicants respectfully submit that a person having ordinary skill in the art would not have been motivated by the prior art to arrive at the present invention with a reasonable expectation of success.

The cited references all fail to describe or suggest an immunoconjugate which comprises in pertinent part a Lewis Y-specific antibody that is internalized by a carcinoma cell with which it reacts. The teachings of Abe et al., Kim et al. and Hellstrom et al. are silent with respect to internalization by carcinoma cells of the antibodies described therein, and these references further fail to contemplate the use of such antibodies in an immunoconjugate as provided by the present invention. Further with regard to the recited feature of the claimed invention that the antibody component of the claimed immunoconjugate is capable of being internalized by a cognate carcinoma cell, these prior art teachings are limited to characterization of immunohistochemical staining patterns by the antibodies described therein using tissue samples that were chemically fixed and then sectioned. In other words, the cells in the tissue samples described in these disclosures are no longer viable and are therefore incapable of internalizing any antibody bound to a cell surface molecule. As such, these references fail to disclose or in any way contemplate whether any antibodies described therein might be internalized following binding to a carcinoma cell surface. Further, these references fail to suggest the desirability of such an internalizing antibody, and the Action does not point to any such disclosure in any of these papers. Further still, these references fail to suggest the desirability of incorporating such an internalizing antibody into the subject invention immunoconjugate.

Abe et al. describe monoclonal antibody AH6, which reacts with the Lewis Y antigen, and these authors merely suggest that AH6 may be useful as a diagnostic agent for colon cancer. Abe et al. fail, however, to in any way suggest an immunoconjugate comprising AH6 joined to a therapeutic agent, nor do Abe et al. teach or suggest a Lewis Y-specific antibody that is capable of being internalized by a carcinoma cell to which it binds, for use in an immunoconjugate. Kim et al. also describe monoclonal antibody AH6 and suggest that AH6 might be useful in management of patients with colorectal cancer, but Kim et al. fail to suggest a Lewis Y-specific antibody that is capable of being internalized by a carcinoma cell to which it binds, for use in an immunoconjugate. Similarly, Hellstrom et al. describe screening a large number of monoclonal antibodies for selective binding to tumor cells such as carcinoma cells, but Hellstrom et al. fail to suggest a Lewis Y-specific antibody, nor do they suggest a Lewis Y-specific antibody that is capable of being internalized by a carcinoma cell to which it binds, nor do they in any way contemplate inclusion of an antibody having such features in an immunoconjugate. Therefore, applicants respectfully submit that motivation to combine the references cited in the Action does not "flow from the nature of the problem," nor from the teachings of the cited references. See *In re Rouffet*, 149 F.3d at 1355, 47 U.S.P.Q.2d 1453.

Moreover, applicants submit that Oldham et al. (1983 *J. Biol. Resp. Modif.* 2:1-37) alone or in combination with Schlom (1991, in *Molecular Foundations of Oncology* [Broder, Ed.] Williams & Wilkins), fail to remedy the deficiencies of Abe et al., Kim et al. and Hellstrom et al. In particular, Oldham et al. and Scholm are merely general disclosures relating to the preparation of immunoconjugates, but none of the references cited by the Examiner suggest the desirability of making an immunoconjugate comprising an antibody that binds specifically to Lewis Y on carcinoma cells and that is capable of being internalized by such cells, nor does the Action point specifically to any such suggestion. Applicants thus submit that any combination of the references cited by the Action would not, at the time of filing, have provided a person having ordinary skill in the art with additional motivation to make the present invention. In this regard, it has been established that "virtually all [inventions] are combinations of old elements," and hindsight may not be used to defeat patentability without some reason being shown to select the elements from the prior art references for combination in the manner claimed. *Rouffet*, 149 F.3d

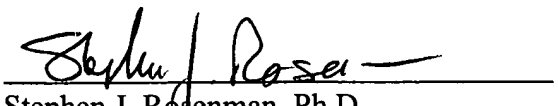
at 1357; 47 U.S.P.Q.2d 1454 (quoting *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 U.S.P.Q. 856, 870 (Fed. Cir. 1983)).

Applicants therefore respectfully submit that the Examiner has not established a *prima facie* case of obviousness, where it is well settled that in order to do so the Examiner must show (1) that the combined references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and where the Examiner must further show (3) that the combined teaching of the prior art references indicates a reasonable expectation of success in arriving at the claimed invention. See, *e.g., In re Mayne*, 104 F.3d 1339, 1341-1342, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997). Furthermore, when a rejection for alleged obviousness depends upon a combination of prior art references, the Examiner must establish that a teaching, motivation, or suggestion to combine the references exists in the prior art, and that the art suggests the desirability of doing so. *In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998); *In re Fritch*, 922 F.2d 1260, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). For the reasons discussed above, there has been no showing of *prima facie* obviousness. Accordingly, applicants respectfully submit that the claimed invention satisfies the requirements of 35 U.S.C. §103 for nonobviousness, and request that the rejection of claims 59-65, 71, 86, and 93 be withdrawn.

In view of the above remarks, Applicants respectfully submit that all of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC



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Copy of Currently Pending Claims

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Currently Pending Claims

59. An immunoconjugate that comprises an antibody joined to a therapeutic agent, wherein the antibody comprises an immunoglobulin or antigen-binding fragment thereof that specifically binds to a Lewis Y cell membrane antigen of a carcinoma cell, wherein upon binding of the antibody to the carcinoma cell, the antibody is capable of being internalized within the cell.

60. The immunoconjugate of claim 59 wherein the therapeutic agent is selected from the group consisting of a cytotoxin, an anti-tumor drug, a radioactive agent, a second antibody, and an enzyme.

61. The immunoconjugate of claim 60 wherein the cytotoxin is a ribosome binding toxin.

62. The immunoconjugate of claim 61 wherein the ribosome binding toxin is ricin A.

63. The immunoconjugate of claim 61 wherein the ribosome binding toxin is an exotoxin.

64. The immunoconjugate of claim 63 wherein the exotoxin is Pseudomonas exotoxin A.

65. The immunoconjugate of claim 63 wherein the exotoxin is truncated to remove the cell-binding domain.

71. The immunoconjugate of claim 63 wherein the amino terminus of the exotoxin has been modified to include a lysine amino acid residue.

86. A pharmaceutical composition comprising a pharmaceutically effective amount of the immunoconjugate of claim 59 and a pharmaceutically acceptable carrier.

93. The immunoconjugate of claim 59 wherein the Lewis Y cell membrane antigen comprises a fucosylated variant of a Lewis Y antigen.